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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/825,958	<b>Applicant(s)</b> CHALIFOUR ET AL.	
	<b>Examiner</b> Kimberly A. Ballard	<b>Art Unit</b> 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 26 July 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 46, 48, 51-53, 55-62, 64, 67-69, 71 and 72 is/are pending in the application.
- 4a) Of the above claim(s) 62, 64, 67-69, 71 and 72 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 46, 48, 51-53 and 55-61 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some    \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>7/26/07; 9/20/07</u> | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 26, 2007 has been entered.

### ***Status of Application, Amendments and/or Claims***

2. Claims 46, 48, 61-62, 64 and 72 have been amended and claims 47, 49-50, 63 and 65-66 have been canceled as requested in the amendment filed on July 26, 2007. Following the amendment, claims 46, 48, 51-53, 55-62, 64, 67-69 and 71-72 are pending in the instant application.

3. Claims 62, 64, 67-69 and 71-72 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 27 April 2006.

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4. Claims **46, 48, 51-53** and **55-61** are under examination in the current office action.

5. Any objection or rejection of record regarding claims 47 or 49-50 is hereby rendered moot in view of Applicants' cancellation of said claims.

***Information Disclosure Statement***

6. Signed and initialed copies of the IDS papers submitted July 26, 2007 and September 20, 2007 are enclosed in this action. The International search and examination reports for PCT/CA00/00515 (on the 09/20/2007 IDS) have been considered, but the individual references contained therein have not been considered. Such references need to be separately listed on an IDS and provided to the Office.

***Priority***

7. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and/or 120 as follows:

For purposes of examination and in determining prior art references, it is noted that the peptides of sequences set forth in SEQ ID NOs: 49-63 were not disclosed in the provisional application 60/168,594 (filed 11/29/1999). SEQ ID NOs: 49-63 were not disclosed until the non-provisional parent application 09/724,842, filed 11/28/2000.

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Additionally, support for the carrier keyhole limpet hemocyanin (KLH, as in instant claim 53) is only found in the parent application 09/724,842 (see p. 7, line 1) and not in the provisional application. Accordingly, for purposes of prior art, the effective filing date of instant claims **46, 48, 51-53 and 55-61** is considered to be the filing date of **28 November 2000**.

### ***Maintained and New Claim Rejections***

#### ***Double Patenting***

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. The provisional rejection of instant claims 46, 48 and 51 over claims 1, 4, 8 and

10 of copending Application No. 10/895,646 is maintained for reasons of record.

In the response filed July 26, 2007, Applicants assert that in view of the amendments and remarks provided in the response, all other grounds of rejection have been met, and thus the provisional double patenting rejection should be withdrawn. Applicants' argument has been considered, but it is not persuasive. As noted below, not all rejections have been overcome. Therefore, the provisional rejection of instant claims 46, 48 and 51 over claims 1, 4, 8 and 10 of copending Application No. 10/895,646, as set forth in the office action dated 06/16/2006, is maintained and held in abeyance until all other rejections are resolved.

10. Applicant is again advised that should claim 60 be found allowable, claim 61 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

***Claim Rejections - 35 USC § 112, first paragraph***

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 46, 48, 51-53 and 55-61 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating an cerebral

amyloid angiopathy or Alzheimer's disease in a subject, does not reasonably provide enablement for a method for preventing an amyloid-related disease and/or Alzheimer's disease as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The claims are broadly drawn to a method for preventing and/or treating an amyloid-related disease in a subject, such as Alzheimer's disease or cerebral amyloid angiopathy, comprising administering to said subject a vaccine for generating anti-amyloidogenic antibodies, wherein said vaccine comprises a peptide and an adjuvant, said peptide consisting of several A $\beta$  peptide sequences, wherein the amino acids KLVF of said peptide consist entirely of [D]-amino acids.

The nature of the invention is the demonstration that antibodies raised against residues 16-21 of A $\beta$  (KLVFFA) are capable of binding to and inhibiting the fibrillogenesis of A $\beta$  peptide *in vitro*. Applicants contend that the antibodies recognize only the non-aggregated form of A $\beta$ , not the aggregated form, and therefore are capable of blocking fibrillogenesis (p. 15). Thus, Applicants disclose that by having such activity "the vaccine

of the present invention 1) prevents A $\beta$  from organizing itself into a fibril and 2) prevents an inflammatory response being triggered by such an antibody binding to an insoluble form, since the antibody is not able to bind to aggregated A $\beta$ ." (p. 15, lines 2-5)

The state of the art also recognizes that while immunization with A $\beta$  peptide or passive immunization with anti-A $\beta$  antibodies have been shown to be effective in transgenic murine models of Alzheimer's disease (AD) (see, for example, Bard et al. *Nature Med.* 2000; 6(8): 916-919, listed on Applicant's IDS), there are many issues that still need to be resolved in immunotherapy of AD in humans (see, for example, De Felice and Ferreira, *Cell Mol Neurobiol.* 2002; 22(5-6): 545-563; and St. George-Hyslop et al. *Nature*, 1999; 400:116-117, listed on Applicant's IDS). For example, subsequent to the effective filing date of this application, clinical trials using A $\beta$  peptide vaccines in AD patients have revealed serious negative side effects of the immunotherapy in a number of the patients, such as inflammation of the CNS, which is indicative of a potential breakdown of the blood-brain barrier and entry of T-cells into the brain (see p. 551 of De Felice et al. 2002; and Münch and Robinson, *J Neural Transm*, 2002; 109: 1081-1087). The art to which the present invention relates is therefore highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficacy.

Applicant extrapolates the prior art findings to assert that immunization with [D]-amino acid A $\beta$  peptides comprising KLVF to subjects having Alzheimer's disease or cerebral amyloid angiopathy (CAA) will prevent such diseases. However, no guidance, prophetic or otherwise, is provided demonstrating that administration of the claimed A $\beta$

peptides to an animal or human effectively results in the prevention of an amyloid-related disease, such as Alzheimer's disease or CAA. Furthermore, "prevention" is understood in the art to encompass total protection from disease or injury. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. The instant specification, however, fails to teach that the immunization with vaccine comprising an A $\beta$  peptide is able to treat human patients having Alzheimer's disease, such as by inhibiting the formation of new A $\beta$  deposits or reducing A $\beta$  levels within the brains of the patients, and in no way demonstrates prevention of such diseases.

Moreover, both at the time of filing and now, effective therapy for the prevention of Alzheimer's has eluded researchers. De Lustig et al. (*Rev in Neurosciences*, 1994; 5: 213-225) report that there is still no adequate preventive strategy and no effective therapies for the pathology, and the disease thus follows an inevitable degenerative course. And a more recent review by Vickers (*Drugs Aging*, 2002, 19(7): 487-494) notes that there is no effective treatment currently available to reverse, slow down or prevent the course of Alzheimer's disease and most other brain diseases and conditions.

Therefore, in view of the breadth of the claims encompassing prevention of amyloid-related diseases, such as the neurodegenerative disorders of cerebral amyloid angiopathy and Alzheimer's disease, the lack of sufficient guidance or data or evidence supporting a preventative effect of the claimed vaccine, the unpredictability in the art of treatment of Alzheimer's disease in general, and the complex nature of the invention,

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one of skill in the art would find that undue experimentation would be required to practice the claimed invention in its full scope.

***Claim Rejections - 35 USC § 103***

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. The rejection of claims 46, 48, 51-53 and 55-61 under 35 U.S.C. 103(a) as being unpatentable over WO 96/28471 by Findeis et al. (published 19 September 1996), in view of WO 99/27944 by Schenk (published 10 June 1999) and as evidenced by Kalaria (*Ann N Y Acad Sci*, 1999; 893: 113-125), is maintained for reasons of record.

In the response filed July 26, 2007, Applicants argue that the Examiner's hypothesis regarding antibodies directed to fibrillogenic portions of A $\beta$  being be more effective than those antibodies directed to non-fibrillogenic regions of A $\beta$  is not supported by any evidence. In contrast, Applicants argue that the use of a peptide as an antifibrillogenic agent involves a totally different mechanism than use of the same peptide for raising neutralizing antibodies against the peptide, and thus one would not be motivated to use as a vaccine a peptide shown to have beneficial effects in inhibiting amyloid fibril formation, because antibodies raised against such an antifibrillogenic peptide would most likely completely prevent the peptide's beneficial antifibrillogenic activity. Applicants present Pike et al. (*J. Neuroscience*, 1993; 13(4):1676-87) as evidence that not all A $\beta$  peptides capable of forming aggregates are suitable to induce an immune response. In this instance, Applicants submit that the Pike reference, which teaches the peptide fragment A $\beta$ 25-35, combined with the Schenk reference would be in direct opposition to the current rejection, because although the peptide would seem a good candidate for a vaccine because the region comprising A $\beta$ 25-35 is important for

fibrillogenesis and is also highly toxic to neuronal cells, Schenk teaches that has "poor immunogenicity". Applicants therefore assert that the fact that the peptides of Findeis are antifibrillogenic does not mean that they would be predicted to be effective immunogens for use in vaccination methods, such as those of Schenk. Applicants further submit that factors directed to the preparation of an effective vaccine (e.g., choice of adjuvants, size of peptide antigen, conjugation of the peptide, presence/absence of D-amino acids), are not addressed in the cited references, which provides further evidence for the non-obviousness of the present claims.

Applicant's arguments filed July 26, 2007 have been fully considered but they are not persuasive. In contrast to Applicants' arguments that a peptide taught by Findeis would not make a good immunogen, it is noted that a peptide comprising the instantly claimed fibrillogenic region of A $\beta$  (KLVF) was used in a vaccine preparation by Schenk to elicit a reasonable and sufficient immune response. Schenk demonstrates that vaccination with the peptide consisting of amino acids 13-28 of A $\beta$ , which comprises A $\beta$ 16-19 (i.e., SEQ ID NO: 13 or KLVF), elicits anti-A $\beta$ 42 antibody titers as high as some N-terminal peptides (e.g., A $\beta$ 1-5) and higher than C-terminal peptides (e.g., A $\beta$ 25-35 and A $\beta$ 33-42) (see Figure 13). Thus, one of skill in the art would reasonably expect that administration of the claimed peptides, and especially the instantly claimed SEQ ID NO: 3 (A $\beta$ 1-35) or SEQ ID NO: 4 (A $\beta$ 1-28), would be capable of inducing an adequate immune response, particularly if the peptide is administered with an adjuvant or other immune-enhancing stimulant. So even in view of the poor immunogenicity of other fibrillogenic regions of A $\beta$ , such as the A $\beta$ 25-35 peptide taught in the Pike and Schenk

references, the skilled artisan would still have a reasonable expectation of successful antibody production using a peptide comprising the KLVF fibrillogenic region of A $\beta$ , which clearly are altogether different than the C-terminal regions of the amyloid- $\beta$  peptide taught by Pike et al., which, expect for SEQ ID NO: 3, are not even encompassed by the instantly claimed peptide sequences.

Additionally, contrary to Applicants' assertions that preparation of an effective vaccine is further evidence of the non-obviousness of the present invention, Schenk presents ample teachings with respect to the use of adjuvants, immunoenhancing agents, and peptide selection, and even compares the antibody titer responses of several adjuvants (see, for example Table 9 on p. 70). Moreover, based on these teachings and the knowledge of vaccine preparations generally available to one of ordinary skill in the art, it would not be beyond the skill or knowledge of the artisan to optimize the vaccination procedures for the administered peptide(s). It would be routine practice to optimize the particular administration parameters to determine the optimal peptide length, adjuvant, timing of administration, conjugation of peptide (or not), etc., and the skilled artisan would be motivated to do so based upon "[t]he normal desire of scientists or artisans to improve upon what is already generally known", see MPEP 2144.05. Thus, absent some demonstration of unexpected results from the claimed vaccine preparation, this optimization would have been obvious at the time of applicant's invention.

With respect to applicants' arguments that there is no motivation to combine the references related to allegedly opposing mechanisms (i.e., that the use of a peptide as

an antifibrillogenic agent involves a totally different mechanism than use of the same peptide for raising neutralizing antibodies against the peptide), the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The skilled artisan would be well aware of the fibrillogenic nature of the A $\beta$  region comprising KLVF, as noted in the teachings of Findeis and as evidenced in the prior art (see, for example, US 6,331,440, US 6,022,859, Wood et al. (*Biochem*, 1995; 34:724-730), and Pallitto et al. (*Biochem*, 1999; 38:3570-3578); all listed on Applicant's IDS). As stated previously, Findeis recognizes that modulation of A $\beta$  aggregation leads to a decreased neurotoxicity of the A $\beta$  fibrils in cells in culture, and thus compounds which interfere with the production of toxic A $\beta$  or APP fragments would be beneficial for *in vivo* treatment of amyloidosis (see column 5, lines 41-54). Findeis thus teaches that compounds having the property of binding to  $\beta$ -amyloid fibrils and/or modulating the aggregation of the fibrils are beneficial. Similarly, Schenk acknowledges that effective treatment of amyloid disease means reducing the amount or level of deposited amyloid aggregates and/or inhibiting the formation of amyloid aggregates (see, for example, pp. 23-24 and Examples I and III), such as by administering fragments of A $\beta$  to induce an immunogenic response against certain epitopes within the  $\beta$ -amyloid peptide. Therefore, in seeking a therapy for amyloid-related disease, the skilled artisan would

have ample motivation to select for agents that inhibit or reduce amyloid aggregation, regardless of the particular mechanism or compound employed to achieve this result.

In combination, the teachings of Findeis and Schenk demonstrate to the artisan that compounds which bind to and inhibit A $\beta$  production and/or aggregation, such as anti-A $\beta$  antibodies, are compounds capable of treating amyloid-related disease. One of skill in the art would also know that administration of a peptide with an adjuvant to a subject will generate an immune response in the form of antibodies directed to the administered immunogen, and Schenk teaches that A $\beta$  peptide in particular will elicit an immune response and B cell activation. The antibodies generated in this response thus become the means for achieving the desired result – in this case, inhibition of amyloid aggregation or reduction of amyloid plaque deposits. Based on the combined teachings and the general knowledge in the art regarding amyloid aggregation, the skilled artisan would thus reasonably expect that antibodies directed to a fibrillogenic portion of A $\beta$  would be more effective to interfere with amyloid fibril formation and thus inhibit amyloid aggregation than antibodies directed to other non-fibrillogenic portions of A $\beta$ . This is also evidenced by the teachings of WO 01/62801 A2 by Holtzman et al., which demonstrate that the monoclonal antibody 266, which was raised against the peptide fragment of A $\beta$ 13-28 and would encompass the KLVF region, is capable of sequestering circulating A $\beta$  and altering the clearance of soluble and bound forms of A $\beta$  in the central nervous system (see p. 5, lines 1-4 and Examples 11 and 12 in particular). Thus, the particular peptides disclosed by Findeis, such as KLVFFA and KLVFF (which are identical to instant SEQ ID NOs: 7 and 15, respectively), which are taught to

interfere with amyloid fibril formation, would be the obvious epitope to use for the generation of anti-fibrillogenic antibodies, and the skilled artisan would be motivated to use these peptides in a vaccination method as taught by Schenk.

Furthermore, regarding Applicants' assertion that there would be no motivation to combine the references under 35 U.S.C. 103(a), it is noted that the recent KSR decision (*KSR International Co. v. Teleflex Inc.*, 550 U.S. --, 82 USPQ2d 1385 (2007)) forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR*, 82 USPQ2d at 1396) (available at [www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf](http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf)). Accordingly, the rejection of claims 46, 48, 51-53 and 55-61 is maintained.

15. The rejection of claims 46, 48, 51-53 and 55-61 under 35 U.S.C. 103(a) as being unpatentable over WO 99/27944 by Schenk, published 10 June 1999, as evidenced by Alberts et al. (Molecular Biology of the Cell, 2<sup>nd</sup> Edition, Garland Publishing Inc., 1989) and Kalaria RN (*Ann N Y Acad Sci*, 1999; 893: 113-125), and in view of Tjernberg et al. (*J Biol Chem*, 1996; 271(15): 8545-8548), WO 96/28471 by Findeis et al., published 19 September 1996, Van Regenmortel et al. (*Curr Opin Biotechnology*, 1998; 9: 377-382), US 4,116,768 to Isowa et al., issued 26 September 1978, and US 6,436,903 B1 to Clayberger et al., issued 20 August 2002, filed 22 May 1996, is maintained for reasons of record.

In the response filed July 26, 2007, Applicants note that the claims have been amended to specify particular peptides, and that none of the references provide any suggestion or motivation to use these specific peptides in the context of the presently claimed invention. Applicants refer to the arguments set forth above with respect to the combination of Findeis, Tjernberg and Schenk – that the references teach inhibition of fibril formation by peptides and use of peptides as vaccine antigens, and these approaches involve completely different and contradictory mechanisms. Applicants assert that no evidence has been provided that would indicate that the peptides of Findeis (or Tjernberg) would be sufficiently immunogenic, as supported by the evidence presented in the Pike reference, not that antibodies against these peptides would have the desired effects. Applicants further note that Schenk does not teach sequences consisting entirely of [D]-amino acids, and there is no suggestion or motivation in the art that such peptides would have the desired beneficial effects of the present invention. Accordingly, Applicants argue that the claimed immunogenic peptides are an unexpected selection over the various peptide fragments suggested by Schenk and others.

Applicants' arguments have been fully considered but they are not persuasive. Applicants' arguments regarding the allegedly opposing technologies of A $\beta$  peptides have been addressed above. In particular, the use of fibrillogenic A $\beta$  peptides for the vaccine preparations in the treatment of amyloid-related disease is not mechanistically contradictory as Applicants present it. As stated above, the skilled artisan would recognize that antibodies directed to a fibrillogenic portion of A $\beta$  would be more

advantageous than antibodies directed to a non-fibrillogenic region of A $\beta$  with regard to interfering with amyloid fibril formation and subsequently inhibiting amyloid aggregation. In fact, Tjernberg states that "a molecule capable of binding to a site in the A $\beta$  molecule being critical for fibril formation, and with an affinity higher than native A $\beta$ , may inhibit amyloid growth and possibly also specifically dissolve amyloid fibrils *in situ*" (see p. 8548, bottom of 1<sup>st</sup> column). One of skill in the art would immediately recognize that "a molecule capable of binding with higher affinity than native peptide" is fairly descriptive of an antibody molecule. Thus, the particular peptides disclosed by Findeis, such as KLVFFA and KLVFF, which are taught to interfere with amyloid fibril formation, would be obvious choices for use in the development of peptide vaccine preparations, such as in the methods taught by Schenk, as the skilled artisan would be motivated to develop antibodies directed against the fibrillogenic region of A $\beta$ . Moreover, as noted above, the artisan would reasonably expect that such peptide vaccines would be effective for the production of antibodies having the desired therapeutic properties, as evidenced by the teachings of Schenk, demonstrating antibody production following immunization with A $\beta$ 13-28, and WO 01/62801 A2 by Holtzman et al., demonstrating the therapeutic effectiveness of an antibody raised against A $\beta$ 13-28.

Futhermore, regarding Applicants' assertion that there would be no motivation to combine the references under 35 U.S.C. 103(a), even assuming *arguendo* that the combined references did not provide such motivational teachings as noted above, it is noted that the recent KSR decision (*KSR International Co. v. Teleflex Inc.*, 550 U.S. --, 82 USPQ2d 1385 (2007)) forecloses the argument that a specific teaching, suggestion,

or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR*, 82 USPQ2d at 1396) (available at [www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf](http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf)).

Finally, in response to Applicants' argument that Schenk does not teach sequences consisting exclusively of [D]-amino acids, the Examiner notes that such teachings were addressed by Findeis, who discloses that anti-fibrillogenic peptides of the invention, such as the A $\beta$  peptide sequences KLVFFA and KLVFF (which are identical to instantly claimed SEQ ID NOS: 7 and 15, and which would also comprise SEQ ID NO: 13 (KLVF) of the instant application), may be modified by substitution of all D-amino acids for all L-amino acids within the compound (p. 17, lines 18-20) (see also p. 17 of the previous office action). Similarly, Van Regenmortel teach the benefits of using peptides constructed entirely of D-amino acids, particularly for the production of immunogenic vaccine preparations. Thus, such all D-amino acid peptides would not be considered an unexpected selection in view of the combined teachings of the above references. Accordingly, claims 46, 48, 51-53 and 55-61 remain rejected as being obvious to the artisan at the time of filing in view of cumulative reference teachings.

### ***Conclusion***

16. No claims are allowed.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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October 10, 2007

/Elizabeth C. Kemmerer/  
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